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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/539,382	03/31/2000	Alison A. McCormick	LSB-001/CIP	9680

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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/539,382	MCCORMICK ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54,56,60-64,72,73,76,77 and 79-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54,56,60-64,72,73,76,77 and 79-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed April 6, 2006 in response to the Office Action of October 6, 2005 is acknowledged and has been entered. Claims 1-53, 55, 57-59, 65-71, 74-75, and 78 have been canceled, and claim 54, 56, 60-64, 72, 73, 76, 77 and 79-89 are under examination.

2. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

4. Claims 54, 56, 60-64, 72, 73, 76 and 81-86 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth on page 2, paragraph 4 of the paper mailed October 6, 2005.

Applicant argues that it is the antigen (a polypeptide) and not the polynucleotide that is used as a vaccine in the presently claimed invention. The argument has been considered but has not been found persuasive because, contrary to applicant's argument, it is not at all clear whether the tumor-specific vaccine is the polynucleotide comprising or the antigen.

Applicant argues that the claims are clear because they are directed to a "tumor-specific vaccine" which defines the tumor being treated by the vaccine. This argument has been considered and has not been found to be persuasive because it is unclear if the vaccine is useful as a tumor-specific vaccine for tumor types other than B-cell lymphoma tumor types. Amendment of the claims to recite, for example "a B-cell lympoma-specific vaccine" would obviate the instant rejection.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 82-86 and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 82 recites the limitation "the polypeptide linker" in the first part (d). There is insufficient antecedent basis for this limitation in the claim.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54, 56, 60-64, 72, 73, 76, 77 and 79-89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding an scFV comprising the VH and VL region of a B-cell lymphoma surface immunoglobulin does reasonably provide enablement for a polynucleotide encoding any epitope of B-cell lymphoma formed by two domains linked together by a polypeptide linker. This means the scFV may comprises any portion or any two domains of the surface immunoglobulin other than the complete VH and VL regions and the linker may be any linker of the broadly claimed sizes.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to the following:

A polynucleotide comprising a nucleic acid sequence encoding a polypeptide epitope of a B-cell lymphoma surface immunoglobulin antigen useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor, and a nucleic acid sequence promoting expression of the polypeptide in a plant cell or plant and a nucleic acid sequence inducing transient replication of said polynucleotide in the cytoplasm, which polypeptide:

(a) includes an epitope or epitopes unique to, or overexpressed by, cells of said tumor, thereby distinguishing said tumor from all other tumors (i) of the same or different histological type, (ii) in said subject or in another member of said subject's species and formed by two domains linked together by a polypeptide linker;

(b) is produced in a plant cell or plant that has been transformed or transfected with said nucleic acid derived from said tumor of said subject;

(c) is obtainable from said plant cell or plant in correctly folded form, with a need for denaturation and renaturation and mimics said epitope or epitopes in their native form; and

(d) is capable of inducing an immune response in mammal, including said subject, so that administration of said polypeptide results in antibody or cell-mediated immune responses to said epitope or epitopes,

wherein the polypeptide linker:

(a) has between one and about 50 residues;

(b) consists of between one and 12 different amino acids, and

(c) facilitates secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell,

(d) and is a member of a randomized library of linkers that vary in size and sequence, said the library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides having the following requirements;

(i) position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet;

(ii) position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; *or*

(iii) position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet

and

(iv) position 1 of each repeated triplet is deoxyadenosine or deoxyguanosine;

(v) position 2 of each repeated triplet is deoxycytidine or deoxyguanosine; and

(vi) position 3 of each repeated triplet is deoxythymidine (claim 54),

wherein said polypeptide is produced transiently in said transformed or transfected plant (claim 56),

the polypeptide comprising two V region domains of said immunoglobulin (claim 60),

the polypeptide comprising two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin (claim 61),

the polypeptide comprising two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin, wherein the part of the V_H region of said polypeptide includes at least one complementarity-determining region (CDR) (claim 62),

the polypeptide comprising two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin, wherein the part of the V_H region of said polypeptide includes at least one complementarity-determining region (CDR), wherein the CDR of the polypeptide is CDR2 (claim 63),

the polypeptide comprising two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin, wherein the polypeptide is a two-domain single chain antibody (scFV) that includes said at least part of the V_H and V_L domains (claim 64),

wherein said immune response is a protective anti-tumor response (claim 72),

wherein on administration to a mammalian host, including said subject, said polypeptide induces a polyclonal anti-idiotypic antibody response or a cell mediated immune response (claim 73),

wherein on administration to a mammalian host, including said subject, said polypeptide induces a polyclonal anti-idiotypic antibody response or a cell mediated immune response, wherein said administration comprises subcutaneous immunization

with at least about 15 µg of said polypeptide antigen three times each about two weeks apart (claim 76)

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wherein the polypeptide is capable of inducing said immune response without a need for adjuvant or other immunostimulatory materials (claim 81),

Wherein said polynucleotide is operably linked to a signal sequence that directs newly synthesized protein to a secretory pathway of the plant and said polypeptide obtainable from said plant cell is secreted from said plant cell (claim 87),

And

a polynucleotide encoding a two domain single chain antibody (scFV) wherein a first domain is linked to a second domain by an amino acid linker that

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(ii) has between one and about 50 residues;

(iii) consists of between one and 12 different amino acids;

(iv) facilitates secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell;

(v) is a member of a randomized library of linkers that vary in size and sequence, and said library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides having the following requirements,

a) position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet;

b) position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet;

c) or position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet,

and

(iv) position 1 of each repeated triplet is deoxyadenosine or deoxyguanosine;

(v) position 2 of each repeated triplet is deoxycytidine or deoxyguanosine; and

(vi) position 3 of each repeated triplet is deoxythymidine (claim 77).

Wherein said scFV includes at least part of the V_H domain and at least part of the V_L domain (claim 79),

Wherein said scFV includes at least part of the V_H domain and at least part of the V_L domain, wherein said domains are those of a surface immunoglobulin epitope of a B-cell lymphoma (claim 80),

Wherein said polynucleotide is operably linked to a signal sequence that directs newly synthesized protein to a secretory pathway of the plant and said polypeptide obtainable from said plant cell is secreted from said plant cell (claim 88).

And

A polynucleotide comprising a nucleic acid sequence encoding a polypeptide epitope of a B-cell lymphoma surface immunoglobulin antigen useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor, and a nucleic acid sequence of a vector capable of transiently replicating in the cytoplasm of and promoting expression of the polypeptide in a plant cell or plant, which polypeptide:

(a) includes an epitope or epitopes unique to, or overexpressed by, cells of said tumor, thereby distinguishing said tumor from all other tumors (i) of the same or different histological type, (ii) in said subject or in another member of said subject's species

b) is produced in a plant cell or plant that has been transformed or transfected with said nucleic acid derived from said tumor of said subject;

(c) is obtainable from said plant cell or plant in correctly folded form, with a need for denaturation and renaturation and mimics said epitope or epitopes in their native form; and

(d) is capable of inducing an immune response in mammal, including said subject, so that administration of said polypeptide results in antibody or cell-mediated immune responses to said epitope or epitopes,

wherein the polypeptide linker :

(a) has between one and about 50 residues;

(b) consists of between one and 12 different amino acids, and

(c) facilitates secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell,

(d) and is a member of a randomized library of linkers that vary in size and sequence, said the library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides having the following requirements;

(*i*) position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet;

(ii) position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; *or*

(iii) position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet

and

(iv) position 1 of each repeated triplet is deoxyadenosine or deoxyguanosine;

(v) position 2 of each repeated triplet is deoxycytidine or deoxyguanosine; and

(vi) position 3 of each repeated triplet is deoxythymidine (claim 82),

Wherein said vector is a plant virus (claim 83),

Wherein said vector contains a subgenomic promoter capable of promoting expression of said polypeptide (claim 85),

Wherein said polypeptide is a two-domain single chain antibody (scFV) that includes the at least part of the V_H and the V_L domains (claim 86),

Wherein said polynucleotide is operably linked to a signal sequence that directs newly synthesized protein to a secretory pathway of the plant and said polypeptide obtainable from said plant cell is secreted from said plant cell (claim 89).

The specification teaches the construction polynucleotides that encode single chain antibodies that mimics the surface Ig of a B-cell lymphoma and includes one or more idiotypic epitopes of that Ig that are uniquely characteristic of that lymphoma (page 8, lines 5-16). The specification further teaches that idiotypes, and their component epitopes, are generally localized in V_H domains of isolated H chains of V_L domains of L chains, wherein idiotypes are more frequently created by the participation of both the H and L chain V regions and may include amino acids from both chains, that that two chains or V domains may interact with one another in such a manner as to stabilize an idiotope that could be entirely on one chain (page 3, lines 4-11). The specification further teaches the expression in plant protoplasts of a polynucleotide encoding an scFV protein comprising both a V_H and V_L region from patient CJ, wherein the linkers were 13-20 amino acids in length (Example 2, Table 1). The specification further teaches the expression in whole plants of a polynucleotide encoding an scFV protein comprising both a V_H and V_L region from patient CJ, wherein the linkers were 13-17 amino acids in length and the use of one of the expressed proteins as an immunogen in mice (Example 3, Table 3). The specification further teaches the expression in whole plants of a polynucleotide encoding an scFV protein comprising both a V_H and V_L region from a mouse lymphoma, and that the protein was able to generate antibodies in mice and protect mice from tumor challenge (Example 5). The specification further teaches that polynucleotides encoding scFV comprising the V_L and VH regions from ten patients for the production of scFV in plants (Example 6, Table 5).

The specification cannot be reasonably extrapolated to enable the scope of the claims because one of skill in the art could not predict that (i) polynucleotides that encode any portion of a B-cell lymphoma surface immunoglobulin antigen, including any two domains or any portion of the V_H region or any portion of V_L region would be useful as a B-cell lymphoma tumor-specific vaccine or (ii) that any size linker would produce functional idiotypes useful as a tumor-specific vaccine.

In the first aspect, as set forth above, the specification teaches that B-cell

lymphoma surface immunoglobulin idiotypes generally comprise the interaction of both the V_H and V_L chains, either by the idiotope being present on both chains or being stabilized by the interaction of the chains. Further, the art teaches that protein chemistry is one of the most unpredictable fields. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (see Bowie et al, Science, 247:1306-1310, 1990, p. 1306, col.2). The specification provides no guidance on structure or residues that are critical to the function of the invention as claimed in the preservation of the idiotypes of the surface immunoglobulin molecules. Although drawn to antibody humanization techniques, the teaching of Gussow et al 1991, Methods in Enzymology 203:99-121) is clearly relevant to the instant rejection. Further, Gussow et al specifically teach that the applicability of antibody humanization techniques relies on, among others, the assumption that the frameworks of the variable domains serve as a scaffold to support the CDRs in a specific way that facilitates antigen binding and further teach that it is of great importance to retain the interactions between the donor CDRs and the acceptor framework as closely as possible to the CDR-framework interactions of the original Mab. Gussow et al. further teaches that the affinity of the first fully humanized antibody CAMPATH1 was nearly 40 fold lower compared to the original rat MAb, apparently because of differences of residues in the framework region of the humanized antibody compared to those of the original antibody, particularly those located close to the CDRs. While the teaching Gussow is directed to antibody binding rather than idiotype preservation, the teaching is clearly instructive in that it suggests the sensitivity of the three dimensional structure of the antigen binding region, and thus the idiotype of the antibody, to amino acid changes. Clearly, alteration of even one amino acid residue can alter the packing of the residues within the molecule as it was demonstrated that mutation of the human Ser 27 to a Phe (the

residue found in the original rat antibody at this position) restored the binding affinity of the humanized antibody close to the original affinity (see page 100). Further, even minor changes in the amino acid sequence of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function (Rudikoff et al, PNAS, USA, 1982, 79: 1979). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of an antibody molecule, and likely the idiotypes contained therein.

In the second aspect, one of skill in the art could not predict that any size linker would produce functional idiotypes useful as a tumor-specific vaccine. Klausner (Biotechnology, 1986, 4:1042-1043) specifically teaches that in order to properly position the antibody fragments in a single chain molecule, the protein linker needs to span about 30-40 angstroms and further teaches that this would require some 15-25 amino acids, but the exact number would depend on the extent to which the linker takes on a secondary structure of its own (see page 1043, 1st column). Given the teaching of Klausner, it is clear that one would not expect that any linker of 1-50 amino acids would function as claimed with a reasonable expectation of success.

In view of the lack of predictably of protein chemistry and antibody modification and the lack guidance with regard to these issues, such as working examples which demonstrate that antibodies comprise less the V_H and V_L region of particular B-cell surface immumoglobulin would preserve idiotypes, or that short linker segments are functional, one of skill in the art could not predict that the invention would function as claimed. Thus, practice of the invention would require undue experimentation.

7. If applicant were able to overcome the rejection under 35 U.S.C. 112, first paragraph, claims 54, 56, 60-64, 72, 73, 76, 81-88 and 89 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotide encoding a polypeptide useful for treating a B-cell lymphoma tumor, does not reasonably provide enablement for a polynucleotide encoding a polypeptide

useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor. This means the tumor may be any tumor, or vaccine may be for a person at risk of developing a tumor.

The claims are set forth above.

The teaching of the specification is as set forth above.

In a first aspect, one cannot extrapolate the teaching of the specification to the enablement of the scope of the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. For example, Gura (1997, Science 278:1041-1042) teaches that researchers face the problem of sifting through potential anti-cancer agents to find ones promising enough to make human clinical trials worthwhile and teaches that, since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para.). Thus, if anti-cancer agents that have success in inhibiting the growth of cancer cells in vitro cannot be predicted to have potential therapeutic success, it certainly cannot be predicted that agents for which no such showing has been demonstrated will be successful in the treatment of cancer. In the instant case, the specification does not provide any working examples (i.e. any in vitro or in vivo evidence) that a B-cell surface immunoglobulin antigen will be useful in treating any type of tumor other than B-cell lymphomas. In a second aspect, one cannot extrapolate the teaching of the specification to the enablement of the scope of the claims because it cannot be predicted that a B-cell surface immunoglobulin antigen will be useful as a tumor specific vaccine in a subject at risk for developing a tumor. The specification does not define individuals at risk of developing a tumor and there is no teaching in the specification as to when the method is to be initiated other than that the prophylactic treatment can be begun before there is any evidence of a tumor. Certainly the majority of the population of the United States has been inadvertently exposed to carcinogenic substances through exposure, for example, to second hand smoke and all of the population has

been exposed to nuclear radiation from the sun. Clearly not all of these individuals or even the majority of these individuals develops a malignancy associated with the exposure and it is not clear how the claimed method would be used for these individuals. Further, although individuals have been identified who have genetic predisposition for developing cancer, it is well known in the art that not all of these individuals eventually develop the disease and that the identification of individuals with genetic risk is a developing, but not yet developed art.

Thus, in view of the unpredictability of the cancer therapeutic arts and the lack of any working examples in the specification that show that that a B-cell surface immunoglobulin antigen will be useful in treating any type of tumor other than B-cell lymphomas, or how to identify an individual at-risk for developing a tumor, it cannot be predicted that a B-cell surface immunoglobulin antigen will be useful in treating any type of tumor other than B-cell lymphomas or that it will be useful as a vaccine for an individual at risk for developing a tumor.

8. No claims allowed.

9. All other objections and rejections recited in the previous Office Action are hereby withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER